REMARKS

Status of the Claims

Claims 1-28, 32, 35-74, 78, 81-91 are pending in the application. Claim 91 has been added herein. Claims 2, 17, 32, 35-74, 78, 81-85 are withdrawn from consideration. Claims 1, 3-16, 18-28 and 86-91 are under examination.

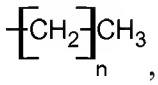
Support for the amendment to claims 1, 7 and 89 can be found, for example, in paragraphs [0024], [0048]-[0054] and [00163] of the specification. Support for new claim 91 can be found, for example, in paragraph [0006] of the specification. No new matter is added.

Examiner Interview

Applicant wishes to thank Examiner Minnifield for the courtesy of an interview, which was extended to Applicant's undersigned representative on October 27, 2010, for which a complete Interview Summary was mailed on October 29, 2010.

Claim Rejection under 35 U.S.C. 112, second paragraph

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as indefinite. According to the Office Action, there is insufficient antecedent basis for the phrase "four to eight" in claim 4. This rejection is respectfully traversed.

Claim 1 requires a synthetic phospholipid compound comprising a plurality of linear alkane groups,  , in which n is independently an integer ranging from 6 to 20. Thus claim 1 defines the *number* of linear alkane groups (i.e., a plurality) as well as the *length* of these groups (n=6 to 20). Claim 4 further defines the *number* of linear alkane groups present (i.e., four to eight) but does not further define the *length* of the groups (i.e., the length remains at n=6 to 20).

For at least the preceding reasons, withdrawal of the outstanding rejection under 35 U.S.C. 112, second paragraph is requested.

Claim Rejection under 35 U.S.C. 112, first paragraph (enablement)

Claims 1, 3-16, 18-28 and 86-88 are rejected under 35 U.S.C. 112, first paragraph, because the specification allegedly does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

According to the Office Action, the specification, while being enabling for an immunogenic composition comprising those components in the immunogenic compositions set forth in Tables 2 and 3A-3C, does not reasonably provide enablement for an immunogenic composition comprising any combination of possible components as set forth in the claims.

With regard to enablement, the Examiner's attention is directed to MPEP 2164.01, a pertinent portion thereof reads as follows:

> Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde,* 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).... See also *United States v. Telectronics, Inc.,* 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988) ("The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.") A patent need not teach, and preferably omits, what is well known in the art....

Thus, the disclosure in the patent application, coupled with information known in the art, must contain sufficient information to enable one skilled in the pertinent art to *make and use* the claimed invention without undue experimentation.

With regard to the description regarding *how to make* the claimed invention, all presently pending claims under examination concern an immunogenic composition that comprises: (a) water; (b) a polymer microparticle; (c) an antigen adsorbed to the microparticle; and (d) a synthetic phospholipid compound. Disclosed throughout the present specification, including the working examples, are methods of making the claimed immunogenic compositions. Regarding phospholipids see, for instance, paragraphs [0064] to [0081] and the references set forth therein; regarding antigens see, for instance, paragraphs [0082] to [0092] and the references set forth therein; regarding microparticles, including how to form them and how to associate species such as antigens and phospholipids with them (e.g., adsorption, entrapment, etc.) see, for instance, paragraphs [0120] to [0137] and the references set forth therein. See also Examples 1-3.

Accordingly, it is respectfully submitted that, based on the present disclosure, one skilled in the art could readily *make* the claimed invention without undue experimentation.

With regard to the description as to *how to use* the claimed invention, the specification describes numerous ways of administering the immunogenic compositions of the claimed invention, including various modes of injection, nasal administration, mucosal administration, intraocular administration, rectal administration, vaginal administration, oral administration, pulmonary administration, and so forth. See, e.g., paragraphs [0145] to [00149] and the references set forth therein, as well as Example 3. In response the Examiner argues as follows:

> However, it is the Examiner's position that the specification does not enable the broad scope of the instantly claimed invention. It is noted that this is not a lack of enablement based on written description, the claimed invention has been described as shown by Applicant's statements above. Applicant has set forth a large genus of immunogenic compositions comprising among other components a very large genus of synthetic phospholipids (see claims 1 and 7-9 for example). For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation.

Of the undue experimentation factors set forth in *In re Wands,* the examiner has focused almost exclusively on the "level of predictability in the art".

As noted above, the specification describes numerous ways of administering the immunogenic compositions of the claimed invention, including various modes of injection, nasal administration, mucosal administration, intraocular administration, rectal administration, vaginal administration, oral administration, pulmonary administration, and so forth.

Furthermore, whether or not a host's immune system is stimulated could be readily determined at the time of the invention by routine experimentation. "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d at 737, 8 U.S.P.Q.2d at 1404 (quoting *Ex parte Jackson*, 217 U.S.P.Q. 804, 807 (Bd. App. 1982)).

Even beyond the above, it is also respectfully submitted that the claims are further enabled based on the fact that the adjuvants are claimed by class (i.e., polymer microparticle and

a synthetic phospholipid compound). Each adjuvant within a respective class would be reasonably expected to behave in a fashion analogous to other adjuvants *within the same class*. For instance, various synthetic phospholipid compounds, including phospholipids like those claimed, act as ligands for a specific class of receptor—specifically, the TLR4 receptor.[1] See, e.g., U.S. Pub. No. 2004/0006242 at paragraphs [0068] *et seq*.

Since the inventors have shown that an exemplary adjuvant from each class can be combined to provide desirable results, one of ordinary skill in the art would be expected to be able to combine other adjuvants from the same classes without undue experimentation.

For at least these above reasons, it is respectfully submitted that the present disclosure is sufficient to enable one of ordinary skill in the art to practice the claimed invention *throughout its scope* without having to engage in undue experimentation. See *In re Wands*.

In view of the above, withdrawal of the rejection of claims 1, 3-16, 18-28 and 86-88 under 35 USC 112, first paragraph, is requested.

Rejection of Claims 89 and 90 under 35 U.S.C. §103(a)

Claims 89 and 90 are rejected under 35 U.S.C. §103(a) as being unpatentable over O'Hagan et al., WO 98/33487 (O'Hagan) in view of Hawkins et al., US 6,290,973 (Hawkins). This rejection and its supporting remarks are respectfully traversed.

For a proper obviousness rejection under 35 U.S.C. 103, the differences between the subject matter sought to be patented and the prior art must be such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. 35 U.S.C. §103. The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. MPEP 2141. " '[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.' " *KSR International Co.* v. *Teleflex Inc.*, 550 U.S. ___, 82 USPQ2d 1385 (2007), quoting *In re Kahn ,* 441 F.3d 977, 988, (Fed. Cir. 2006).

[1] TLR4 is a member of the Toll-like receptor (TLR) family of receptors; in humans, the TLR family comprises ten known receptors, designated TLR1-10.

It should be noted that the prior art reference (or references when combined) must teach or suggest all the claimed features. "When determining whether a claim is obvious, an examiner must make 'a searching comparison of the claimed invention – *including all its limitations* – with the teaching of the prior art.' ... Thus, 'obviousness requires a suggestion of all limitations in a claim.' ..." *Ex parte Wada and Murphy*, BPAI Appeal No. 2007-3733, January 14, 2008 (emphasis in original) (citations omitted). In addition, there must be a reasonable expectation of success. See MPEP 2143.02.

The Examiner has asserted that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine the teachings of O'Hagan with Hawkins to make an immunogenic composition comprising water, polymer microparticle, antigen adsorbed to microparticle, and various synthetic phospholipids "for the purpose of immunizing a subject to increase or enhance immunogenic activity, immune response or stimulate/enhance protection against an infectious antigen for example."

In support of her position, the Examiner has relied upon the following case law from MPEP 2144.06:

> "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be *prima facie* obvious.). See also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held *prima facie* obvious).

The present application, however, does not constitute a case in which *Kerkhoven* and its ilk can be relied on in support of a legal conclusion of obviousness. For example, *Kerkhoven* involved "two compositions each of which is taught by the prior art to be useful for the same purpose". Moreover, the claims in *Kerkhoven* required "no more than the mixing together of two conventional spray-dried detergents." 626 F.2d at 850. Similarly, *In re Crockett* involved two components, each of which was known to promote the formation of a nodular structure in cast

iron, and *Ex parte Quandranti* involved mixing two compositions, each of which was known to be a herbicide.

The present facts are not analogous. Although polymer microparticles and synthetic phospholipid compounds may be broadly identified as "adjuvants," the art of record, including O'Hagan and Hawkins, do not teach or suggest that these adjuvants would be interchangeable/useful for the same purpose.

For example, O'Hagan teaches at page 2 that "[p]articulate carriers with adsorbed or entrapped antigens have been used in an attempt to elicit adequate immune responses. Such carriers present multiple copies of a selected antigen to the immune system and promote trapping and retention of antigens in local lymph nodes. The particles can be phagocytosed by macrophages and can enhance antigen presentation through cytokine release." There is no teaching or suggestion in O'Hagan or Hawkins, on the other hand, that synthetic phospholipids such as those presently claimed could be used as particulate carriers for adsorbed or entrapped antigens. Thus, O'Hagan and Hawkins clearly do *not* teach "two compositions … useful for the same purpose" and the preceding case law is not on point.

Apparently referring to MPEP 2141 (and *KSR*), the Examiner has also stated the following (emphasis added):

> The Supreme Court further stated that: When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a ***predictable*** variation, §103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill. Id. at ___, 82 USPQ2d at 1396. When considering obviousness of a combination of known elements, the operative question is thus "whether the improvement is more than the ***predictable*** use of prior art elements according to their established functions." Id. at ___, 82 USPQ2d at 1396.

Unlike *KSR*, which pertained to a predictable technology (i.e., automotive pedals), the present invention pertains to the chemical arts (and more particularly, the biochemical arts), which are unpredictable.[2]

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[2] It should be kept in mind that since the inventors have shown that an exemplary adjuvant from each class claimed (specifically, a polymer microparticle and a synthetic phospholipid compound) can be successfully combined, one of ordinary skill in the art would be expected to be able to combine other adjuvants from the same classes without undue experimentation. See above.

Indeed, the Federal Circuit, post *KSR*, has indicated that the obviousness bar is high for chemical inventions: "[t]o the extent an art is unpredictable, as chemical arts often are, *KSR*'s focus on...'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." *Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd,* 533 F.3d 1353, 1359 (Fed. Cir. 2008).

See also, *Ortho-McNeil Pharmaceutical Inc. v. Mylan Laboratories Inc.*, 520 F.3d 1358 (Fed. Cir. 2008), in which the Court affirmed the district court's denial of Mylan's motion for summary judgment of invalidity under § 103. The Court found that the ordinarily skilled artisan would have to have some reason to select among several unpredictable alternatives, which supported the conclusion that "this clearly is not the easily traversed, small and finite number of alternatives that *KSR* suggested might support an inference of obviousness." *Id.* at 1364.

Analogous to *Ortho-McNeil Pharmaceutical Inc., supra,* to arrive at the claimed invention, one of ordinary skill would have to have some reason to select among the myriad unpredictable alternatives known in the art. Instead, the Examiner has merely used Applicant's present specification and claims as a road map to arrive at the claimed invention.

In view of the foregoing, it is respectfully submitted that, without undue hindsight gained upon review of the present specification and claims, the presently pending claims are unobvious in view of the teachings of O'Hagan and Hawkins. See, e.g., MPEP 2142, second paragraph, *Akzo N.V. v. U.S. International Trade Commission*, 808 F.2d 1241, 1480-81, 1 U.S.P.Q.2d, 1241, 1246 (Fed. Cir. 1986), *cert. denied,* 482 U.S. 909 (1987), and *Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 874, 228 U.S.P.Q. 90-99 (Fed. Cir. 1985).

Nor would there be a reasonable expectation of success. In this regard, Applicant had previously presented R. Edelman, *Molecular Biotechnology*, 21(2) 2002, 129-148 (Edelman), which demonstrated that those of ordinary skill in the art would have recognized that (a) every adjuvant (including microparticle adjuvants) has a complex and often multi-factorial immunological mechanism, usually poorly understood in vivo, (b) many determinants of adjuvanticity exist and (c) each adjuvanted vaccine is unique. Accordingly, the choice of an adjuvant frequently depends upon experimental trial and error. *Id.*

Moreover, the present claims are directed to a *combination* of adjuvants (i.e., a polymer microparticle and a synthetic phospholipid). In this regard, see, page 278 of previously attached A.R. Spickler et al., *J Vet Intern Med* 2003; 17: 273-281 (Spickler), wherein under the heading

"Combined Adjuvants," the following is stated: "The result of combining adjuvants depends on the mechanism of action and toxicity of each individual component. Combinations may be better, similar to, or worse than the individual components."

Consequently, one of ordinary skill in the art would not have a reasonable expectation of success.

Furthermore, even assuming for the sake of argument that a *prima facie* case of obviousness exists, such a *prima facie* case of obviousness would be overcome by a showing of unexpected results. It is well settled that a patent applicant can rebut a *prima facie* case of obviousness by a showing of "unexpected results", e.g., by showing that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the art would have found surprising or unexpected. See, e.g., *In re Soni,* 34 U.S.P.Q.2d 1684, 1687 (Fed. Cir. 1995).

For example, based on the Edelman and Spickler references cited above, one of ordinary skill in the art would not reasonably expect an improved immune response from the combination of adjuvants presently claimed.

However, as seen from Table 2 in the present specification, by adding the phospholipids set forth in claims 89 and 90 in various forms, the inventors were able to increase the total IgG response relative to PLG with adsorbed MenB by about 4.2 to 8.8 times (and relative to PLG with adsorbed MenB plus soluble CpG by about 2.4 to 5.1 times). Such results are unexpected in view of the prior art.

For at least these reasons, withdrawal of the Examiner's rejection of claims 89 and 90 under 35 U.S.C. 103(a) is requested.

CONCLUSION

Applicant submits that all pending claims are in condition for allowance, early notification of which is earnestly solicited. Should the Examiner be of the view that an interview would expedite consideration of this Amendment or of the application at large, the Examiner is requested to telephone the Applicant's attorney at (703) 433-0510 in order to resolve any outstanding issues in this case.

FEES

The Office is authorized to charge any fees that may be due and owing as a result of this Response to deposit account number 50-1047.

Respectfully submitted,

Dated: November 19, 2010
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